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*a*CEA and *a*MUC1-Directed Immunotherapy for Metastasis

[This project evaluates the use of anti-CEA and anti-MUC1 antibodies for inhibition of homotypic and geterotypic adhesion and the reduction of metastasis]

One uniform characteristic of all cancers is their ability to invade host tissues and produce metastases. Although many advances have been made in the diagnosis and treatment of cancer, our inability to prevent the formation of metastases is a major cause of deaths from cancer. An improved understanding of the metastatic process and specific properties unique to metastatic cells has opened several avenues of investigation for new therapeutic approaches.

Metastatic cells penetrate blood vessels and are then transported to a new site. They then arrest in the capillary bed of receptive organs and permeate into the new tissue. While in the circulation, cells tend to aggregate into clusters to avoid detection and attack by the immune system. One tumor-associated protein responsible for cells adhering to each other is carcinoembryonic antigen **(CEA).** This same protein is also involved in cancer cells adhering to cells lining blood vessels (endothelial cells), a necessary step for cell arrest in a new tissue. We postulate that blocking CEA with an antibody will prevent the formation of cell clusters in the circulation, making them more open to immune attack. Use of antibody to CEA should also reduce the adherence of cells to the endothelium. This issue will be addressed using cell culture systems and whole animal-metastasis models for human colonic and pancreatic cancer. Once the appropriate site to be blocked on CEA is identified, we will administer anti-CEA antibodies to mice and determine whether the number of metastatic sites is reduced and whether median survival time of the animal is increased.

Another molecule that appears to be important in various steps of the metastatic process is MUC-1. We postulate that the use of an appropriate MUC-1 antibody will block adhesion between tumor cells and a) endothelial cells and b) the layer beneath the vessel called the basement membrane and thus reduce the metastatic spread of tumor cells. The appropriate site of MUC1 to be blocked will again be identified and anti-MUC-1 antibodies will then be administered to mice with metastatic clonic or pancreatic tumors to determine if survival time can be increased. If both anti-CEA and anti-MUC-1 antibodies provide promising results, the effect of blocking both CEA and MUC-1 together will be determined.

All the antibodies needed for researchers at our research have made these studies center and are available in house. Both animal models have been developed at our center and are reproducible.